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POSITION STATEMENT

# Management of Ischemic Heart Disease in Patients With Heart Failure

## *JACC: Heart Failure* Position Statement

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### HIGHLIGHTS

- Ischemia testing can be used to define ischemic myocardium burden, or the physiologic significance of CAD. The choice of testing may depend on patient factors and local expertise. Randomized trials have not reported that ischemia testing strategies improve, or are associated with, improved clinical outcomes.
- GDMT is an essential part of management for all patients with HF and should include beta-blocker, ARNI (preferred) or ACEI or ARB, MRA, and SGLT2 inhibitor in patients with HFrEF and for patients with HFpEF with a history of ischemic cardiomyopathy, SGLT2 inhibitor should be utilized. Additional therapies such as MRA, ARNI, or ARB can be considered in some clinical settings to reduce the risk of HF hospitalization.
- Revascularization with CABG improves outcomes in stable patients with an ischemic cardiomyopathy and severe extensive coronary artery disease.
- PCI in HFrEF has not been reported to reduce clinical events. In an unblinded trial, PCI improved short- but not long-term exercise tolerance and quality of life. In patients with an ischemic cardiomyopathy and extensive coronary artery disease with anatomy suitable for PCI, physicians may consider PCI when CABG is not an option but this approach has no trial data to support it.
- Randomized data do not support the routine use of viability or ischemia testing as primary criteria by which patients are selected for percutaneous or surgical revascularization. Viability testing may refine the risk assessment for patients in whom decisions regarding revascularization remain uncertain. Viability tests may also provide valuable information about scar burden that can be used to risk stratify patients with severe ischemic cardiomyopathy and possibly guide decisions such as ICD insertion or help with decision making around partial revascularization.

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## ABBREVIATIONS AND ACRONYMS

**ACEI** = angiotensin-converting enzyme inhibitor

**ACS** = acute coronary syndrome

**ARB** = angiotensin receptor blocker

**ARNI** = angiotensin receptor neprilysin inhibitor

**CABG** = coronary artery bypass graft

**CAD** = coronary artery disease

**CMR** = cardiac magnetic resonance

**FFR** = fractional flow reserve

**GDMT** = guideline-directed medical therapy

**HFrEF** = heart failure with reduced ejection fraction

**HFpEF** = heart failure with preserved ejection fraction

**ICD** = implantable cardioverter-defibrillator

**LVEF** = left ventricular ejection fraction

**MI** = myocardial infarction

**MRA** = mineralocorticoid receptor antagonist

**PCI** = percutaneous coronary intervention

**PET** = positron emission tomography

**SGLT2** = sodium-glucose cotransporter 2

**SPECT** = single-photon emission computed tomography

## ABSTRACT

Coronary artery disease remains a common cause of morbidity and mortality for patients with heart failure, both in the acute and chronic settings. The management decisions for these patients are complex and are often driven by the clinical setting (ie, acute vs chronic disease) and predominant symptoms (angina vs heart failure). However, there remain significant gaps in the knowledge/evidence around optimal timing and implementation of medical therapy and the role and selection of patients for revascularization. Suggested considerations for clinical practice are provided based on the current body of evidence with emphasis on ongoing gaps in knowledge for future clinical research in this area. (JACC Heart Fail. 2025;13:102731) © 2025 by the American College of Cardiology Foundation.

Ischemic heart disease remains a major global health challenge, with rising incidence driven by aging populations and metabolic diseases. Although age-standardized rates are declining in some regions, total cases are expected to increase due to demographic changes. For many patients, the sequelae of either an acute ischemic syndrome or chronic coronary artery disease (CAD) is the development of ventricular dysfunction and heart failure (HF). The medical management of patients with HF involves the optimization of guideline-directed medical therapy (GDMT) in parallel with secondary prevention of CAD. However, there are many ways that HF and CAD intersect (**Figure 1**) and current limitations in our understanding of phenotypes can make management decisions complex. This is particularly true in decisions around coronary revascularization in which there remain questions about the optimal evaluation, timing, and type of revascularization to consider. This document aims to provide a current understanding of the intersection of chronic CAD and HF, with practical recommendations for evaluation and management in relevant clinical settings. Acute coronary syndromes (ACSs) and cardiogenic shock, although critically important, are beyond the scope of this position statement. We highlight what is known from within the boundaries of clinical evidence and outline the many unanswered clinical questions for future research in this field (**Figure 2**).

## EPIDEMIOLOGY OF ISCHEMIA IN HF

Ischemic heart disease is the most common cause of HF across the western world. There is significant global geographic heterogeneity in prevalence estimates; in general, significant epicardial CAD has been reported more frequently in patients with heart failure with reduced ejection fraction (HFrEF) compared with preserved ejection fraction (HFpEF).[1] Pooled U.S. longitudinal cohort data estimate that 6% to 32% of people aged ≥45 years will develop HF within 5 years after a first myocardial infarction (MI), with the

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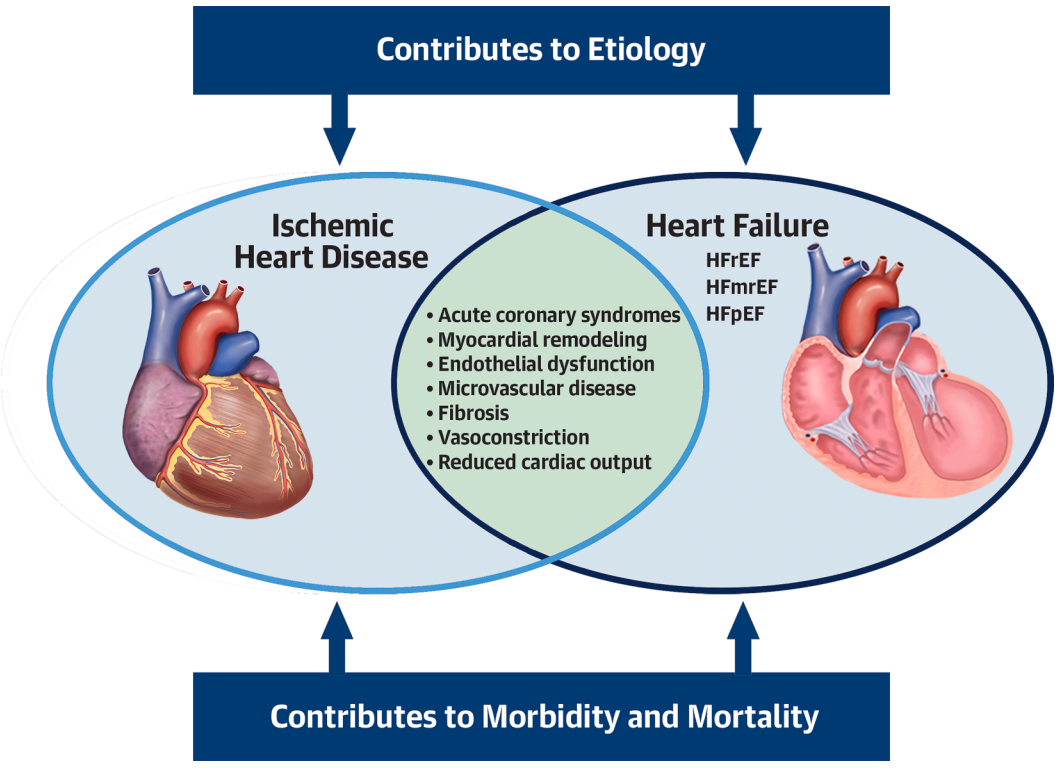
**FIGURE 1** Overlap of Syndromes Associated With HF in the Setting of CAD




CAD is a common cause of HF and contributes to the morbidity and mortality of HF prognosis. Similarly, the presence of clinical HF increases the morbidity of patients with CAD. CAD = coronary artery disease; HF = heart failure; HFmrEF = hear failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

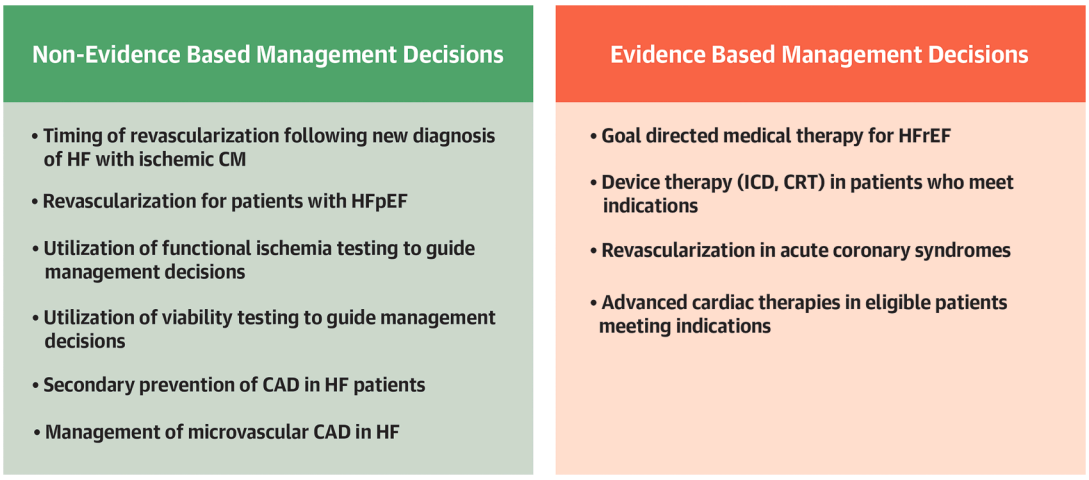
highest risk for Black men and women up to age 74 years.[2] Advancements in early detection and treatment of MI have reduced the risk of death and development of HF by 50% over the past 3 decades.[3] In the contemporary PARADISE-MI (Prospective ARNI versus ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events after Myocardial Infarction), first HF hospitalization occurred in 6%-7% of patients in each of the treatment arms at a median follow-up of 23 months.[4]

Preexisting HF also substantially increases the risk of adverse cardiovascular (CV) outcomes after ACS. The CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) program demonstrated an acute coronary event rate of 5.9 events per 100 patient years in a cohort of 7,599 patients with HF, with similar rates for those with left ventricular ejection fraction (LVEF) >40% compared with LVEF ≤40%.[5] Early mortality after MI in this cohort was marked with 30% dying within 30 days after MI.[5] Observational data from the GRACE (Global Registry of Acute Coronary Events) study (1999-2007) similarly demonstrated this persistent disproportionately high mortality burden for patients with HF who experience a subsequent ischemic event with nearly a 2-fold increased risk of in-hospital mortality[6] and more than a 2-fold increase in 6-month mortality.[7] Encouragingly, outcomes have improved over the past 2 decades,[8] largely attributed to increased implementation of guideline-recommended secondary preventive care.

## PHENOTYPES OF HF BEYOND ACSs

There remains significant heterogeneity in the development of clinical HF with concurrent CAD as well as a lack of longitudinal data on ischemic heart disease progression, event frequency, phenotype evolution (eg, silent ischemia to acute events), HF development, and cardiogenic shock. Patients can be diagnosed with HF in the setting of known CAD, such as that which occurs following an ACS or cardiogenic

**FIGURE 2 Examples of Common Types of Decision Making, With and Without Evidence as a Guide, in the Management of Patients With Ischemic Heart Disease and HF**


Non-Evidence Based Management Decisions
• Timing of revascularization following new diagnosis of HF with ischemic CM
• Revascularization for patients with HFpEF
• Utilization of functional ischemia testing to guide management decisions
• Utilization of viability testing to guide management decisions
• Secondary prevention of CAD in HF patients
• Management of microvascular CAD in HF
Evidence Based Management Decisions
• Goal directed medical therapy for HFrEF
• Device therapy (ICD, CRT) in patients who meet indications
• Revascularization in acute coronary syndromes
• Advanced cardiac therapies in eligible patients meeting indications

CM = cardiomyopathy; CRT = cardiac resynchronization therapy; other abbreviations as in Figure 1.

shock. However, for many patients, CAD is only diagnosed after the development of HF, and determining the relative contribution of CAD to an existing cardiomyopathy can be challenging. It is critical to understand how these different phenotypes can impact HF management and subsequent decision making around revascularization and acknowledge the limitations in the available evidence base to guide these decisions.

## HF WITH CHRONIC CAD.

**CAD with HFrEF.** CAD is a progressive and dynamic disease that requires active intervention from prevention to treatment to reduce poor outcomes. CAD is the most prevalent cause of HFrEF, and epidemiologic data suggest that ~60%-70% of patients with HFrEF have underlying ischemic heart disease as the primary etiology. The risk increases with age, male sex, diabetes mellitus, and hypertension. In chronic CAD, repeated episodes of subclinical or overt myocardial ischemia can lead to myocyte necrosis, fibrosis, and adverse ventricular remodeling. Compared with patients with non-ischemic HFrEF, patients with CAD and HFrEF have higher mortality, more frequent hospitalizations, and worse overall outcomes.[9,10] In patients with newly diagnosed HFrEF, the presence and extent of CAD has been demonstrated to have significantly greater prognostic impact among women than men.[11] Given the high prevalence of CAD in patients with HF, and the implications on prognosis, an evaluation for CAD burden should be considered in all incident HF patients, particularly with low ejection fraction (EF), and other risks for CAD.[12]

**CAD with HFpEF.** Although reduced EF is a known risk factor for developing HF following an ACS, a significant portion of patients with ACS-HF have an EF >40%.[13,14] Myocardial ischemia and fibrosis frequently result in diastolic dysfunction in patients with CAD, and previous pathologic studies have demonstrated that >60% of patients with HFpEF have coexisting CAD.[15] In addition to CAD predisposing to HFpEF, recent studies have identified that extra coronary calcification in asymptomatic individuals is also a significant risk factor for incident HFpEF. This highlights some of the potential vascular and proinflammatory contributions to the HFpEF phenotype.[16] Few studies have reported on the association between CAD and survival in HFpEF; however, a previous report from the Duke Cardiovascular Databank in 2000 links multivessel CAD to increased mortality in patients with HF symptoms and an EF >40%.[17] The ETICS (Epidemiologie et Therapeutique de L'Insuffisance Cardiaque dans la Somme) registry prospectively followed 591 consecutive patients for 10 years following an incident HF admission in 2000. CAD was an independent predictor of all-cause and CV death in patients with HFrEF; however, patients with HFpEF with CAD were at a greater risk of sudden death.[18] Whether these

phenotypic differences contribute to differences in response to medical and interventional treatment for chronic CAD in these patients is not known. The role of revascularization in patients with chronic CAD and HFpEF in the absence an ACS presentation remains a challenge, particularly in patients with significant comorbid disease. Longitudinal outcome data and novel strategies are needed to help guide management decisions around benefit/risk of revascularization.

**HF WITH NONOBSTRUCTIVE CAD.** Contemporary research highlights the pathophysiological phenotypes of nonobstructive CAD syndromes, such as ANOCA (angina with no obstructive coronary arteries), INOCA (ischemia with no obstructive coronary arteries), and MINOCA (myocardial infarction with no obstructive coronary arteries). These syndromes, which predominantly affect women, are associated with coronary microvascular dysfunction and heightened coronary vasoreactivity, which can lead to major adverse CV outcomes, including HF. Incidence rates for adverse outcomes are ~3% annually, with 1-year mortality for MINOCA approaching 5%.[19,20] There is no role for revascularization in patients with nonobstructive CAD syndromes complicated by HF, and little evidence to guide clinicians on the optimal management of these patients.

**HF WITH CONCOMITANT CHRONIC "BYSTANDER" CAD.** HF and atherosclerosis commonly coexist; they can develop from shared genetic predispositions, but also from lifestyle-related risk factors and comorbidities.[21] It is also important to distinguish left ventricular (LV) systolic dysfunction resulting from overt ischemia secondary to severe CAD vs HF with LV systolic dysfunction resulting from other causes with incidental CAD that is not felt to be physiologically or functionally significant. Bystander CAD refers to the presence of anatomical coronary artery lesions that are not directly responsible for the myocardial dysfunction. This has a profound downstream therapeutic implication because patients with "true" ischemic cardiomyopathy might benefit from revascularization and secondary prevention measures, whereas the management of patients with "bystander" CAD in the setting of HF is an area of clinical uncertainty. With the growth and availability of noninvasive evaluations for anatomic CAD, increasing numbers of patients with HF are being identified with concomitant CAD, with uncertain clinical or physiologic significance.

Felker et al[22] historically evaluated a large cohort of patients with symptomatic HFrEF and CAD to identify the most prognostic features associated with CAD in the setting of HF. They identified a proportion of patients traditionally felt to have "ischemic cardiomyopathy" with a prognosis similar to those with a nonischemic etiology; these patients had single-vessel disease, no history of MI or revascularization, and considered them to have HF "out of proportion" to their degree of CAD. They proposed a definition of ischemic cardiomyopathy that included: 1) a history of MI or revascularization; 2) >75% stenosis of left main or proximal left anterior descending artery; or 3) >65% stenosis in ≥2 epicardial vessels.[22]

Identification of "bystander" CAD remains a challenge; however, it can be suspected when wall motion abnormalities do not correspond to vascular territories involved, cardiac magnetic resonance (CMR) demonstrates diffuse fibrosis without subendocardial infarction, or viability or ischemia testing does not demonstrate reversible ischemia or significant scar. Furthermore, those with normal epicardial coronary arteries can have evidence of subendocardial or transmural enhancement on CMR, indistinguishable from patients with known CAD and previous infarct. This was identified in 13% of 90 CMR studies done in patients with HF and LV dysfunction. In this cohort of patients, all had risk factors for CAD and none had a clinical history of acute MI. The authors hypothesize that this represents recanalization after an occlusive coronary event or embolization, and should be considered "ischemic" in origin despite the insignificant findings on coronary angiography.[23] How this affects management decisions remains to be identified.

It was previously shown that even nonobstructive CAD among patients with HFrEF is associated with worse clinical outcomes compared with those with normal coronary arteries.[24] How to quantify and mitigate this elevated risk with ischemia testing in this population remains unclear. Future studies should explore noninvasive cardiac imaging modalities that can estimate the burden of bystander CAD among patients with HF and correlate these findings with clinical outcomes (**Table 1**).

## THE DIAGNOSTIC EVALUATION OF ISCHEMIA AND CAD IN PATIENTS WITH HF

There are varying approaches to the evaluation of patients with HF of presumed or established ischemic etiology. Investigations can be tailored to evaluate anatomic disease (invasive coronary angiography, coronary computed tomography angiography with or without fractional flow reserve [FFR]),

**TABLE 1 Clinical Features to Consider When Attributing CAD to Etiology of LV Systolic Dysfunction**

| | Suggestive of Causative CAD | Suggestive of Incidental/Bystander CAD |
|---|---|---|
| Prior MI or angina | Yes | No |
| Regional wall motion abnormality | Focal | Global |
| LGE on MRI | Subendocardial/transmural | Mid-wall or none |
| Perfusion defects | Present | Absent |
| Angiography | Lesions match wall motion abnormality | Lesions unrelated to wall motion abnormality |

CAD = coronary artery disease; LGE = late gadolinium enhancement; LV = left ventricular; MRI = magnetic resonance imaging.

or the functional burden of ischemia (exercise/pharmacologic stress testing with echo, CMR, or nuclear imaging). These approaches are not always mutually exclusive and can provide complementary/additive information. A traditional approach to determine the burden of CAD in a patient with HF is to proceed with anatomic imaging. However, occasionally functional testing is used initially to determine the severity of ischemia when contemplating decisions around potential candidacy for revascularization before anatomic imaging.[25] This strategy continues to be used clinically, despite the lack of evidence to support ischemia-directed decision in improving outcomes following revascularization. A careful evaluation of ischemia among patients with HF requires a multidisciplinary heart team approach including the patient and their family/caregivers with emphasis on shared decision making[26] around management options, particularly for revascularization. Real-world data show that a minority of patients with HF receive a diagnostic work-up for CAD, particularly in the setting of older age or increased comorbidities.[27-29] A summary of the societal recommendations for invasive and noninvasive ischemia and/or viability testing in patients with HF and suspected/established CAD is provided in Table 2 of this document.[12,30-33]

When ischemia testing is performed, it should be customized to local protocols and expertise, availability of imaging resources, and individualized to the patient.[34,35] Importantly, these diagnostic tests may provide data on different aspects of myocardial perfusion and ischemia burden. Integrating and

**TABLE 2 Recommendations on Invasive and Noninvasive Workup Among Patients With HF and Potential for Coronary Revascularization**

| Statement/Recommendation | Class of Recommendation and Level of Evidence | Society |
|---|---|---|
| Invasive work-up | | |
| ICA is recommended in patients with HF and angina despite pharmacological therapy or symptomatic ventricular arrhythmias | Class I, Level of Evidence: B | ESC[30] |
| ICA may be considered in patients with HFrEF with an intermediate-high pretest probability of CAD and the presence of ischemia in noninvasive stress tests | Class IIb, Level of Evidence: B | ESC[30] |
| ICA is recommended in patients with congestive HF due to systolic dysfunction with angina or with regional wall motion abnormalities and/or scintigraphic evidence of reversible myocardial ischemia when coronary revascularization is considered | Class I, Level of Evidence: B | AHA/ACC/SCAI[32] |
| ICA is recommended in patients with HF refractory to drug therapy or complicated with angina pectoris, or those who experienced symptomatic ventricular arrhythmia or cardiac arrest | Class I, Level of Evidence: C | JCS/JHFS[33] |
| ICA may be considered in patients in whom HF is suspected to be caused by ischemia | Class IIa, Level of Evidence: C | JCS/JHFS[33] |
| Noninvasive work-up | | |
| CTCA should be considered among patients with low-intermediate pretest probability of CAD or those with unclear results of noninvasive stress tests to rule out coronary artery stenosis | Class IIa, Level of Evidence: C | ESC[30] |
| Noninvasive stress imaging modalities including CMR, stress echocardiography, SPECT, and PET may be considered for the assessment of myocardial viability in patients with CAD before the decision on revascularization | Class IIb, Level of Evidence: B | ESC[30,31] |
| Patients with HF and CAD who are candidates for coronary revascularization, noninvasive stress imaging methods including stress echocardiography, SPECT, CMR, or PET may be considered for detection of myocardial ischemia to help guide coronary revascularization | Class IIb, Level of Evidence: B | AHA/ACC/HFSA[12] |
| SPECT using thallium chloride or technetium-labeled tracers is recommended to assess myocardial ischemia and myocardial viability in patients with ischemic cardiomyopathy | Class I, Level of Evidence: B | JCS/JHFS[33] |
| Stress echocardiography may be considered to assess myocardial viability in patients with HFrEF | Class IIa, Level of Evidence: B | JCS/JHFS(33) |
| FDG PET may be considered in patients who cannot be assessed adequately with other procedures | Class IIb, Level of Evidence: C | JCS/JHFS[33] |
| Exercise testing may be considered to detect reversible myocardial ischemia and investigate the cause of dyspnea | Class IIb, Level of Evidence: C | ESC[30] |

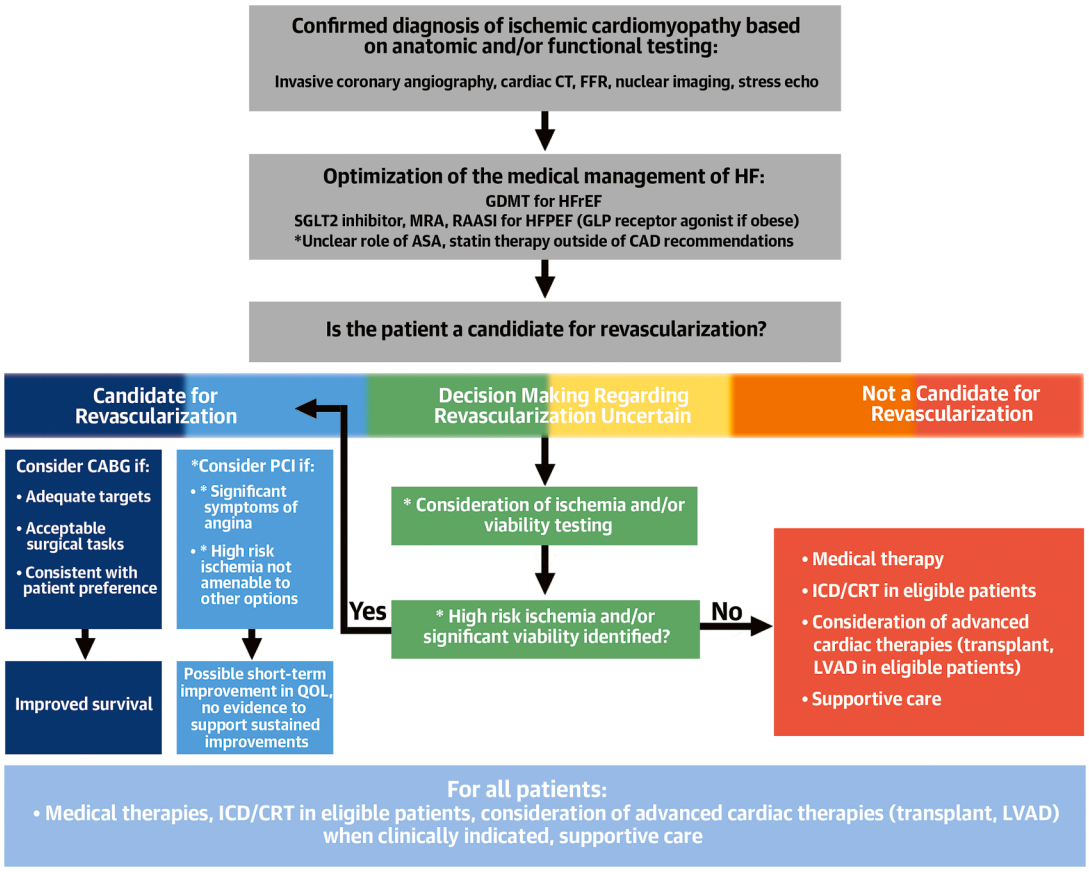
ACC = American College of Cardiology; AHA = American Heart Association; CMR = cardiac magnetic resonance; CTCA = computed tomography coronary angiography; ESC = European Society of Cardiology; FDG = fludeoxyglucose; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HFSA = Heart Failure Society of America; ICA = invasive coronary angiography; JCS = Japanese Circulation Society; JHFS = Japanese Heart Failure Society; PET = positron emission tomography; SCAI = Society for Cardiovascular Angiography and Interventions; SPECT = single-photon emission computed tomography; other abbreviation as in Table 1.

comparing these data across different testing modalities can be a challenge when trying to facilitate further management.[36] This heterogeneity in ischemic testing modalities is also reflected in heterogeneity of recommendations across international guidelines. European and North American HF guidelines do not recommend a specific noninvasive imaging method, whereas Japanese guidelines give Class 1, Level of Evidence: B recommendation for single-photon emission computed tomography (SPECT) using thallium chloride or technetium-labeled tracers for the purpose of ischemia and myocardial viability assessment in patients with ischemic cardiomyopathy and a lower class of recommendation for stress echocardiography and fludeoxyglucose positron emission tomography (PET) scanning.[33] Preliminary reports from the AIMI-HF (IMAGE-HF Project I-A: Cardiac Imaging in Ischemic Heart Failure) study failed to demonstrate differences in the cardiac clinical composite endpoint with the use of advanced imaging modalities (cardiac PET or CMR) as compared with SPECT for ischemia testing among patients with HF (unpublished data by L. Mielniczuk, September 25, 2025). There are no data to support the superiority of one noninvasive imaging modality over another in the prediction of survival among patients with HF following revascularization.[37,38]

Randomized controlled trials and derived subanalyses failed to show that the degree of inducible myocardial ischemia portends meaningful impact on relevant clinical outcomes among patients with ischemic HF. A sub-analysis of the STICH (Surgical Treatment for Ischemic Heart Failure) trial showed no interaction between the presence/extent of ischemia and benefit for revascularization over medical therapy.[39,40] A potential benefit of myocardial revascularization was shown in the sub-study of ISCHEMIA (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches), which analyzed 398 patients with HF or moderate LV systolic dysfunction at baseline. This analysis suggested that patients with an LVEF between 35% and 45% with a history of anginal symptoms experienced better clinical outcomes when the initial treatment strategy was invasive compared with conservative therapy and this was not the case among patients without HF or LV dysfunction at baseline.[41] Of note, 86% of patients with HF and LV dysfunction in that sample had a moderate-to-severe ischemia on stress imaging or exercise treadmill testing while slightly more than 50% had CCS (Canadian Cardiovascular Society) II-III class angina. However, this was a post hoc sub-analysis in an unblinded study with a very small number of events; therefore, these results should be interpreted cautiously. More recently, the prognostic impact of inducible ischemia on stress perfusion CMR was reported from REVIVED-BCIS2 (Revascularization for Ischemic Ventricular Dysfunction-British Cardiovascular Intervention Society 2 Trial). In this analysis there was no relationship among ischemic burden, clinical outcomes, and randomized treatment allocation (optimal medical therapy with or without percutaneous coronary intervention [PCI]). Interestingly, there was also no interaction between angina score and ischemic burden.[42] The high event rates in this study reflect the high-risk nature of this patient population, and challenges common paradigms about the use of routine ischemia-guided imaging to guide decisions regarding revascularization. However, it needs to be acknowledged this was a post hoc analysis and that REVIVED-BCIS2 was designed as a treatment study and not designed to evaluate the impact of imaging on outcomes. Patients had to have viability to get into this study, and were not selected based on ischemia burden, and definitions of ischemia were based only on the size of the defect and not the severity of the perfusion defect.

Taken together, the present body of evidence does not support routine functional ischemia testing for the purpose of prognosis and risk estimation among HF patients with ischemic cardiomyopathy. However, the evidence is limited and is compounded by significant heterogeneity in the patient population (severity of HF, severity of anginal symptoms), diagnostic modalities, and definitions of ischemia used, as well as downstream medical and/or surgical management. Because of these pitfalls, the proper patient selection for revascularization remains challenging. In patients with HF and angina despite guideline-directed medical therapy, an investigation to determine any contribution related to myocardial ischemia is warranted in order to revascularize significant CAD to improve symptoms and to potentially prolong survival. Important clinical practice considerations are listed in the next section and **Table 2** provides a summary of the guideline recommendations for the use of cardiac imaging in the diagnosis of CAD in HF. The **Central Illustration** demonstrates an algorithm for integrating imaging into decision making for revascularization, highlighting the multiple decision points that are not evidenced based.

**CENTRAL ILLUSTRATION** **Suggested Approach to Decision Making Around Revascularization in Patients With Ischemic Heart Failure, Integrating Management Considerations That May or May Not Be Supported by a Substantial Clinical Evidence Base**


Confirmed diagnosis of ischemic cardiomyopathy based on anatomic and/or functional testing:
Invasive coronary angiography, cardiac CT, FFR, nuclear imaging, stress echo
Optimization of the medical management of HF:
GDMT for HFrEF
SGLT2 inhibitor, MRA, RAASI for HFPEF (GLP receptor agonist if obese)
*Unclear role of ASA, statin therapy outside of CAD recommendations
Is the patient a candidate for revascularization?
Candidate for Revascularization
Decision Making Regarding Revascularization Uncertain
Not a Candidate for Revascularization
Consider CABG if:
• Adequate targets
• Acceptable surgical tasks
• Consistent with patient preference
*Consider PCI if:
• * Significant symptoms of angina
• * High risk ischemia not amenable to other options
* Consideration of ischemia and/or viability testing
Yes
* High risk ischemia and/or significant viability identified?
No
• Medical therapy
• ICD/CRT in eligible patients
• Consideration of advanced cardiac therapies (transplant, LVAD in eligible patients)
• Supportive care
Improved survival
Possible short-term improvement in QOL, no evidence to support sustained improvements
For all patients:
• Medical therapies, ICD/CRT in eligible patients, consideration of advanced cardiac therapies (transplant, LVAD) when clinically indicated, supportive care

**Mielniczuk LM, et al. JACC Heart Fail. 2025;13(12):102731.**

*Clinical decisions that are not supported by significant evidence. ASA = aspirin; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CRT = coronary resynchronization therapy; CT = computed tomography; FFR = fractional flow reserve; GDMT = guideline-directed medical therapy; GLP = glucagon-like peptide; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; ICD = implantable cardioverter-defibrillator; LVAD = left ventricular assist device; MRA = magnetic resonance angiography; PCI = percutaneous coronary intervention; QOL = quality of life; SGLT2 = sodium-glucose cotransporter 2; RAASI = renin-angiotensin-aldosterone system inhibitor.

### CONSIDERATIONS FOR CLINICAL PRACTICE.

- When: To define the burden of CAD through either anatomic or physiologic testing in a patient with either: 1) new diagnosis of HF with a moderate-high probability of CAD; and/or 2) a patient with HF who has angina/angina equivalent.
- Why: Anatomic testing can be used to define coronary anatomy and potential targets for revascularization. Functional testing can identify ischemic myocardium burden or physiologic significance of CAD that may be incorporated into decision making regarding management to guide potential revascularization.
- How: Use of individual patient factors (eg, ability to exercise, renal function, allergies to contrast, claustrophobia) and available interpretation expertise to guide the choice of testing, including

**TABLE 3 Information That Can Be Obtained Through Ischemia Testing of Patients With HFrEF and Clinical Considerations**

| Anatomy of CAD | Extent of Ischemia and Functional Relevance of CAD | Objectivization of Symptoms | Factors Affecting Ischemia Testing of Choice |
|---|---|---|---|
| Defining coronary anatomy through means of CTA or ICA<br>Defining the atherosclerotic burden across coronary arteries through means of CTA or ICA<br>Differentiating "true" ischemic cardiomyopathy chiefly caused by atherosclerotic coronary disease vs bystander nonobstructive coronary disease | Defining and quantifying the extent of myocardial ischemia by using stress echocardiography, SPECT, stress CMR<br>Hybrid imaging such as use of PET/CTCA or SPECT/CT can provide integrative information on both perfusion and anatomical characteristics<br>ICA accompanied with FFR - determining the functional relevance and hemodynamic significance of coronary lesions thus guiding decision on revascularization | Methods such as exercise treadmill stress testing can provide useful information on exercise tolerance and symptom reproduction<br>This method might be helpful to determine severity of HF symptoms in an objective fashion | Severity of HF symptoms<br>Ability to exercise<br>Presence of significant comorbidities such as chronic kidney disease<br>Safety of radiation and contrast agents |

CTA = computed tomography angiography; CT = computed tomography; FFR = fractional flow reserve; other abbreviations as in Tables 1 and 2.

stress echocardiography, SPECT, stress CMR, PET/computed tomography coronary angiography, SPECT/computed tomography coronary angiography, or coronary angiography with physiologic testing (instantaneous wave-free ratio, FFR) (Tables 3 and 4).

## THE EVALUATION OF MYOCARDIAL VIABILITY IN PATIENTS WITH HF

Ischemic heart disease can lead to chronic systolic HF, but this does not always represent irreversible damage. Myocardial stunning and myocardial hibernation are 2 mechanisms that are believed to be involved in the development of dysfunctional but viable myocardium that has yet to develop irreversible cell death. Stunning refers to transient depression of myocardial contractile function due to episodes of hypoperfusion that recovers days to weeks after restoration of perfusion.[35,37] Hibernating myocardium reflects the down-regulation of cardiac function as an adaptation to chronic reduction in coronary flow reserve.[43] As it was first described, a clinical diagnosis of hibernation could be made only in retrospect, if recovery of regional contractile function was observed to have occurred following revascularization of flow-limiting coronary disease subtending that area. The desire to develop a prospective correlate of hibernation (in order to select patients for revascularization) led to the concept of myocardial viability, based on imaging features that confirm 1 or more of evidence of contractile reserve, preservation of membrane integrity, preservation of cellular metabolism, or absence of transmural scarring.[40] Each characteristic can be interrogated by using different imaging modalities in patients with HF (Table 5): dobutamine stress echocardiography, SPECT, PET, and CMR. It is difficult to compare and contrast how well each of these modalities predicts recovery following revascularization for several reasons. First, the tests vary appreciably in the sensitivity and specificity for detecting viability. Second, it is difficult to characterize the quality and extent of revascularization of viable myocardium in a given

**TABLE 4 Clinical Scenarios to Guide Anatomic or Functional Testing of CAD in Patients With HF**

| Scenarios in Which Anatomic Testing of CAD (Coronary Angiography With or Without iFR, FFR, CTA) May Be Helpful | Scenarios in Which Functional/Physiologic Testing of CAD (Stress Echo, Stress CMR, SPECT, PET) May Be Helpful |
|---|---|
| High probability of CAD where definition of anatomy required for anticipated revascularization | Identification of ischemia burden that may impact decisions around the following:<br>Medical management<br>Noncardiac surgical risk assessment<br>Need for invasive coronary angiography |
| Low probability of CAD (consider CTA to "rule out" CAD in diagnostic work-up) | Correlation of anginal-equivalent symptoms with ischemia burden<br>Need to define probability of CAD in a patient with contraindication to contrast-enhanced diagnostic testing |

iFR = instantaneous wave-free ratio; other abbreviations as in Tables 2 and 3.

**TABLE 5 Noninvasive Imaging Modalities to Assess for Myocardial Viability**

| | Mechanism | Advantages | Disadvantages |
|---|---|---|---|
| DSE | Low-dose (2.5-5 μg/kg/min) dobutamine infusion causes improved function in viable myocardium<br>With higher doses, a decrease in myocardial function can be seen, and this biphasic response may be more predictive of recovery with revascularization | Widely available<br>Lower cost<br>No radiation exposure | Poor acoustic windows<br>High interobserver variability |
| SPECT | Thallium-201 is a potassium analog that is actively transported across cell membrane in viable myocytes<br>Viable myocytes may not initially demonstrate thallium update, but may do so on delayed imaging (4-24 hours), which is termed redistribution<br>99mTc-sestimibi can also be used and has comparable accuracy as thallium-201 | Widely available<br>More data available compared with other modalities | Lack of standardization given numerous protocols<br>Delay between rest and redistribution images leads to longer duration of test<br>Low spatial resolution (cannot assess transmurality of tracer distribution) |
| $^{18}$F-FDG PET | Rest myocardial perfusion imaging obtained first<br>In areas that lack resting perfusion, uptake of $^{18}$F-FDG that indicates preserved glucose metabolism signifies viability | High spatial resolution | Less widely available<br>Higher cost than DSE and SPECT<br>Requires fasting period prior to scan |
| CMR | Different parameters have been studied but most widely used is the extent of LGE<br>After injection, gadolinium diffuses into the interstitial space of nonviable muscle and remains there<br>Accumulation of gadolinium defines a scar, with tissue that does not have LGE is considered viable<br>Transmurality >50% is indicative of nonviable myocardium[2] | High spatial resolution allowing for identification of subendocardial infarction and determine transmural extent of infarction<br>Provide additional structural information | Most expensive<br>Patient comfort (claustrophobia)<br>Interference from implantable devices<br>Advanced renal disease may preclude gadolinium administration |

DSE = dobutamine stress echocardiography; other abbreviations as in Tables 1, 2, and 3.

case, as the latter depends on a variety of procedural and patient-level factors; hence, it can be difficult to discern if the failure of recovery was due to inadequacies of the viability test or suboptimal restoration of myocardial reserve. Furthermore, viability is often considered a binary variable, although it is well recognized that a continuous range of viability exists at a segmental and patient level.

Many historical observational, single-center, and nonrandomized studies have demonstrated the ability of noninvasive testing to predict improved myocardial performance following revascularization.[44] A meta-analysis by Allman et al[45] investigated the use of PET, SPECT, and dobutamine stress echocardiography in patients with systolic HF and severe CAD and reported that viability was associated with lower rates of annual mortality with revascularization. A more recent meta-analysis focusing on CMR identified 24 prospective studies and determined delayed contrast enhancement (LGE) with gadolinium provided the highest sensitivity and negative predictive value for predicting improved LV function after revascularization.[46] These early clinical studies set the landscape for the routine use of viability testing in HF. However, interpretation and application of these data are hampered by multiple important considerations that limit applicability to current clinical practice:

- Observational nature of these studies, such that patients undergoing revascularization had a fundamentally different baseline risk profile to those who were managed with medical therapy alone.
- Heterogeneous definitions of viability and outcomes.
- Significant changes in the medical management of HF over time.
- Significant changes in surgical and interventional techniques.

Previous clinical trials have been published to determine if viability testing before revascularization can improve clinical outcomes in patients with systolic HF (Table 6).[40,47,48] A study by Siebelink et al[49] from 2001 suggested that there were no differences in either patient management or cardiac event-free survival when patients with ischemia were randomized to either SPECT or PET imaging; however, this study was not specifically quantifying viability or hibernation, and only approximately one-third had HFrEF.[49] PARR-2 (Positron emission tomography And Recovery following Revascularization phase 2) demonstrated that a PET-based strategy to guide revascularization decisions did not improve outcomes over standard of care. Although physicians who interpreted PET scans provided

**TABLE 6 Major Randomized Trials of Viability Testing Prior to Revascularization in Systolic HF**

| Clinical Trial | Viability Modality | Patient Population | Design | Findings |
|---|---|---|---|---|
| PARR-2[47] (n = 430) | FDG PET | LVEF ≤35%<br>CAD being assessed for revascularization | Patients randomized to management assisted by PET vs standard care<br>In PET group, the imaging team provided recommendation to proceed with revascularization or not based on PET scan, but the ultimate decision was up to the treating physician<br>Primary endpoint: Composite of cardiac death, MI, or recurrent hospitalization for cardiac cause, within 1 y | Composite event was not significantly reduced in PET arm vs standard arm (30% vs 36%)<br>Post hoc analysis revealed that when only including patients in PET group in which the treatment recommendations were followed, there was significant reduction in primary endpoint |
| STICH Viability Substudy[39] (n = 601) | SPECT and/or DSE | LVEF ≤35%<br>CAD amenable to CABG | In this substudy of STICH, all patients underwent viability testing<br>Patients randomized to CABG with medical therapy vs medical therapy alone<br>Primary endpoint was death from any cause over median follow-up of 10.4 y | CABG plus medical therapy was associated with significantly lower incidence of death than medical therapy alone<br>No significant interaction was observed between the presence or absence of viability and the beneficial effect of CABG |
| REVIVED-BCIS2[48] (n = 700) | All 4 modalities | LVEF ≤35%<br>Extensive CAD amenable to PCI<br>Presence of viability in at least 4 dysfunctional myocardial segments | Patients randomized to PCI plus medical therapy vs medical therapy alone<br>Primary composite endpoint was death from any cause of HF hospitalization | No difference in composite endpoint between 2 groups (37% in PCI vs 38% in medical therapy)<br>No improvement in LVEF with PCI<br>Extent of viability did not correlate with primary outcome |

CABG = coronary artery bypass surgery; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PARR-2 = Positron emission tomography And Recovery following Revascularization phase 2; PCI = percutaneous coronary intervention; REVIVED-BCIS2 = Revascularization for Ischemic Ventricular Dysfunction; STICH = Surgical Treatment for Ischemic Heart Failure; other abbreviations as in Tables 2 and 5.

recommendations regarding revascularization, those decisions were not always followed. Post hoc analysis showed that when only patients in whom the PET-guided recommendations were followed were included in analysis, there was a significant improvement in the primary outcome. Furthermore, an additional post hoc analysis showed that those patients with greater degrees of myocardial perfusion-metabolism (ie, more hibernating myocardium) had a significant benefit with revascularization.[50] The benefit of coronary artery bypass graft surgery (CABG) was studied in the STICH trial, which included a substudy of 601 patients who underwent discretionary viability testing. Although the overall study showed the benefit of CABG, there was no interaction between the presence or absence of viability and the clinical benefits of surgical revascularization at 10 years of follow-up. Patients with viability had a small increase in LVEF. It is important to acknowledge that this was not a randomized study of viability, and that 80% of patients enrolled had significant myocardial viability, limiting the ability to assess the relationship between viability status and outcome. Both PARR2 and the STICH viability study were conducted before the era of our current GDMT approach for HFrEF. Finally, REVIVED-BCIS2 assessed the benefits of PCI in patients with systolic HF and evidence of viability and found no benefit of PCI over optimal medical therapy. Furthermore, there was neither evidence of interaction between the extent of viability and the effect of PCI on the primary and secondary outcomes nor any association between the extent of viable myocardium and the likelihood of clinical outcomes or improvement in LV systolic function.[51] A prespecified substudy showed a clear association between the extent of myocardial scar and the likelihood of all-cause death, CV death, and likelihood of LV recovery, indicating a prognostic utility in viability testing.

None of these 3 trials showed that viability testing correlates with improvement in clinical outcomes with revascularization. However, 2 of the studies did not include patients without viability and the third (STICH) had relatively few patients without viability.[35] Notwithstanding the limitations and lack of evidence to support a routine use of viability testing in revascularization, selected use of viability testing may be considered in patients in whom decisions around revascularization and subsequent risk/benefit ratios are uncertain, particularly in the presence of very significant impairment of systolic function and/or large end diastolic volumes. A viability study should never be used for clinical decision making in isolation of other important parameters (including indication, patient risk, potential for alternative therapeutic options, and anticipated outcomes). The 2022 ACC (American College of

**TABLE 7 Considerations for Choice of Modality in Viability Testing**

| | |
|---|---|
| Moderate LV dysfunction | Any modality with local expertise |
| Severe LV dysfunction | Nuclear methods (SPECT, PET) or CMR (late gadolinium enhancement) which are more sensitive than contractile reservice |
| Renal failure or CMR incompatible devices | Avoid CMR or gadolinium |
| Critical left main or proximal 3-vessel disease | Avoid dobutamine |
| Equivocal or negative results on another viability test, in which certainty is needed to completely rule in (or out) viability | Consider CMR or PET which are highly sensitive methods |

Abbreviations as in Tables 1 and 2.

Cardiology)/AHA (American Heart Association)/HFSA (Heart Failure Society of America) guidelines emphasize that the routine use of viability testing is not recommended for all patients with HF; however, it can be considered in select patients if it can influence decisions regarding revascularization strategies.[12]

### CONSIDERATIONS FOR CLINICAL PRACTICE.

- Randomized data do not support the routine use of viability testing as the primary criterion by which patients are selected for percutaneous or surgical revascularization.
- Viability testing such as CMR may provide valuable information about scar burden that can be used to risk stratify patients with severe ischemic cardiomyopathy and possibly guide decisions such as implantable cardioverter-defibrillator (ICD) insertion. Although this may be useful in clinical practice, current guidelines do not incorporate CMR findings into the decision-making algorithm for ICD therapy.
- In patients who have a clinical indication for revascularization (such as those with limiting angina or have presented with ACS), regional viability data for procedural planning might prove useful at identifying target vessels for bypass grafting or PCI.
- Multiple parameters should be taken into consideration when choosing the type of viability test, including, but not limited to, local practice and expertise, body habitus, and renal function (Tables 7 and 8).

## MEDICAL TREATMENT OF ISCHEMIA AND ISCHEMIC HEART DISEASE

Patients with ischemic cardiomyopathy benefit from medical therapy for both HF and for CAD. In patients with HFrEF, there is strong level of recommendation for quadruple GDMT, including HF-specific beta-blockers, angiotensin receptor neprilysin inhibitors (ARNIs) or angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter 2 (SGLT2) inhibitors. In patients with HFpEF, there is evidence for benefit in using SGLT2 inhibitors, MRAs, and ARNI or ARBs.[52]

Some of these HF medical therapies have specific benefits in patients with CAD. Beta-blockers are recommended in patients with CAD to reduce the symptoms of angina. Both beta-blockers and ACEI/ARBs have shown a mortality benefit in patients with acute MI in the setting of reduced EF.[53] Recent data from the REDUCE-AMI (Randomized Evaluation of Decreased Usage of Beta-Blockers after Acute Myocardial Infarction) study demonstrated no long-term benefit of beta-blocker therapy in all-cause death or MI in patients who underwent early coronary revascularization and had preserved LVEF.[54] Similarly, in a recently published systematic review, beta-blockers did not confer additional mortality benefits in revascularized patients without reduced EF.[16] ACEI/ARBs are also indicated in common CAD comorbidities including hypertension, diabetes, and renal dysfunction. However, in the absence of other indications, the role of ACEIs post MI in patients with preserved LV function is less established. SGLT2

**TABLE 8 Clinical Considerations to Guide the Use of Viability Testing**

| Clinical Scenarios in Which Viability Testing May Be Helpful | Clinical Scenarios in Which Viability Testing Is Unlikely to Be of Benefit |
|---|---|
| Decisions around management are uncertain | High-risk coronary anatomy with suitable revascularization targets |
| Chronic total occlusions and/or complexities in coronary anatomy | Poor candidacy for complete revascularization |
| Multiple comorbidities with moderate or high estimated periprocedural risk | Low or intermediate estimated periprocedural risk |
| Moderate-large perfusion defects suggesting scar that could be hibernating myocardium | Strong preference for revascularization based on patient/provider/heart team preference |
| | No or limited comorbidities |

inhibitors have a strong benefit for the reduction of major adverse CV events, largely due to a reduction in CV death and HF events, regardless of baseline diabetes, HF, and renal disease.[55] Early routine use of empagliflozin following acute MI in patients with HF risk factors and LVEF <45% was not shown to have a significant effect on the primary outcome of first hospitalization for HF or all-cause mortality in the EMPACT-MI (A Study to Test Whether Empagliflozin Can Lower the Risk of Heart Failure and Death in People Who Had a Heart Attack [Myocardial Infarction]) study. It was, however, associated with a statistically significant reduction in both first and total HF hospitalizations.[56]

There are limited data to support the medical management of CAD in patients with HF. Although antiplatelet therapy is used following a PCI, clinical trials of long-term use of aspirin and other antiplatelet therapies in HF have been either inconclusive or limited. Previous observational studies have demonstrated that aspirin use is associated with an increased risk of incident HF in patients with or without a prior history of CV disease. Clinical trials of aspirin vs placebo in HFrEF are limited and inconclusive and absent for HFpEF. There has been much debate about the value of aspirin in HF with some proposing detrimental effects.[57,58] In addition, recent data on lipid-lowering therapy in chronic HF has also had disappointing results. Although statins play an important role in the management of CAD to prevent HF,[59] 2 large trials of statins vs placebo in established HFrEF (one with both CAD and HFrEF [CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure)][60] and one with 50% with CAD and HFrEF [GISSI-HF (Effects of n-3 PUFA and Rosuvastatin on Mortality-Morbidity of Patients With Symptomatic CHF)])[61] were both neutral. A post hoc analysis of CORONA suggested that statins might reduce total HF hospitalizations. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors did not prevent HF hospitalizations in a meta-analysis of 23 trials.[62] No trial has been conducted to investigate statins in established HFpEF.

There does not seem to be a benefit to adding niacin, fenofibrate, or omega-3 fatty acids in addition to statin therapy.[63] Colchicine has been shown to decrease CV events in patients with chronic CAD; however, it should be used with caution for patients with renal or hepatic impairment, and studies in HF are currently ongoing.[64-66]

**CONSIDERATIONS FOR CLINICAL PRACTICE.**

- For patients with HFrEF secondary to ischemic cardiomyopathy, the use GDMT including HF-specific beta-blocker, ARNI (preferred) or ACEI or ARB, MRA, and SGLT2 inhibitor should be utilized to maximally tolerated and recommended doses (Class I Recommendation, 2022 AHA/ACC/HFAS Guideline for the management of HF).[12]
- For patients with HFpEF with a history of ischemic cardiomyopathy, SGLT2 inhibitor should be used, and MRA, ARNI, or ARB therapy can be considered in indicated clinical scenarios to reduce risk of HF hospitalization (Class IIa/IIb Recommendation, 2022 AHA/ACC/HFAS Guideline for the management of HF)

## TIMING OF MEDICAL THERAPY AND REVASCULARIZATION IN PATIENTS WITH LV DYSFUNCTION

For patients with HFrEF, it is of utmost importance to start and titrate GDMT to improve morbidity and mortality. However, consideration of revascularization may delay the initiation or titration of most classes of GDMT due to concerns about renal function, hypotension, or other side effects of drug therapies. There is no evidence to guide clinicians about the optimal timing of revascularization following the initiation of GDMT in patients with ischemic HF. Whereas it is recommended to refer patients for CABG if they have CAD and LVEF <35%,[67] GDMT optimization is critical and may change the risk profile for patients with ischemic cardiomyopathy. A period of GDMT optimization and improvement in heart function may improve surgical mortality for patients who ultimately undergo surgical revascularization. Thus, for patients with stable CAD, a strategy of optimal GDMT before revascularization can be employed and cardiac function can be reevaluated when clinically indicated. Although there are no data to support this recommendation, this approach of GDMT optimization then reevaluation is similar to other interventions in HFrEF, such as ICD insertion or percutaneous mitral valve interventions.

There may be patients with unstable or high-risk features in which revascularization may not be safely delayed; this includes patients with ACS, symptoms refractory to medical therapies, and those unable to tolerate GDMT due to high-risk features such as low blood pressure or renal dysfunction. For

these patients, GDMT should be started as soon as possible in the perioperative period, with aggressive medication titration postrevascularization.

**CONSIDERATIONS FOR CLINICAL PRACTICE.**

- Consider optimizing GDMT for up to 3 months before revascularization in patients with CAD and LVEF <35% in the absence of ACS, left main disease, or clinical instability.

## REVASCULARIZATION IN ISCHEMIC HEART DISEASE

The management of patients with ischemic cardiomyopathy includes GDMT (see the Medical Treatment of Ischemia and Ischemic Heart Disease section), augmented by coronary revascularization. The decision to proceed with coronary revascularization and the mode of revascularization will depend on several key factors including the extent and location of the disease, the degree of LV dysfunction and size, the presence and nature of symptoms, and the goals for revascularization and may be strongly influenced by patient utilities or preferences. Several clinical trials have examined the role of coronary artery revascularization for the treatment of patients with an ischemic cardiomyopathy.[48,68-70] These studies provide important perspectives regarding the indications for and benefits of revascularization in this subset of patients.

A subgroup analysis of the CASS (Coronary Artery Surgery Study) trial examining outcomes in 160 patients (20.5% of the randomized trial participants) with an LVEF between 35% and 49% demonstrated a greater survival with CABG compared with minimal medical therapy at 7 years of follow-up in the group of patients with triple-vessel disease and reduced LVEF.[68] Although this study provides supportive evidence to proceed with CABG in patients with an ischemic cardiomyopathy and a mild to moderately reduced EF who meet the trial enrollment criteria, the sample size of the sub-study was small, patients with LVEF <35% were excluded, and the medical therapy for HF management >40 years ago was primitive.

The STICH trial was designed to address the benefits of CABG in patients with more severe LV dysfunction, enrolling patients with an ischemic cardiomyopathy and an LVEF of ≤35%. A total of 1,212 patients with CAD were randomized to a strategy of surgical revascularization (with or without resection of ventricular aneurysm) and medical therapies to treat HF, or medical therapy alone.[70] Roughly 60% of patients had 3-vessel disease and two-thirds of patients had severe disease of the proximal left anterior descending artery. At a median follow-up of 56 months, the primary endpoint consisting of all-cause mortality was not significantly different between the 2 groups. Notably, there was an initial upfront risk of death with CABG at 30 days that was 3 times greater than the observed mortality in the medical therapy arm. This was offset by a greater survival with CABG in longer follow-up. Before the analysis and reporting of the primary study outcomes, the study protocol was amended to include an additional 5 years of follow-up. In this extended study (STICHES [The STICH Extension Study]), a survival benefit was noted with CABG with a 16% lower all-cause mortality (HR: 0.84 [95% CI: 0.73-0.97]; $P = 0.02$) during a median follow-up of 9.8 years.[69] As seen in the earlier CASS trial, a significant interaction between the benefits of CABG over medical therapy and extent of disease was noted. Although the findings reported in the extended study support a role for CABG, it is important to recognize that this benefit may not be realized until 5-10 years after surgery and therefore appropriate selection of patients is needed. In the STICH trial, the mean age of enrolled patients was ~60 years, and when planning surgery in an older subset of patients we can only extrapolate the benefits of CABG reported in the STICH trial.

The REVIVED (Revascularization for Ischemic Ventricular Dysfunction) trial[48] was designed to demonstrate that a strategy of revascularization with PCI on background GDMT would be superior to GDMT alone at reducing the combined rate of all-cause mortality or hospitalization for HF, in patients with significant CAD and an ischemic cardiomyopathy. Secondary outcomes included a measurement of LVEF at 6 and 12 months and quality of life scores using the Kansas City Cardiomyopathy Questionnaire (KCCQ). One consideration for this trial was that because of a potential for a lower upfront risk from PCI (as compared with the early hazard with CABG reported in the STICH trial), the benefits of revascularization would be apparent at a shorter duration of follow-up. Enrollment criteria for this trial included an LVEF of ≤35% with extensive CAD (defined by a BCIS [British Cardiovascular Intervention Society] jeopardy score of ≥6) that was amenable to PCI and significant viability noted on noninvasive imaging studies. To put things in perspective, a BCIS score of 12 indicates extensive disease jeopardizing the entire myocardium. Exclusion criteria included CCS class 3 or 4 angina, recent acute infarction, or hemodynamic or electrical instability. In this trial of 700 patients, roughly 40% of enrolled patients had 3-vessel disease and ~14% of enrolled patients had involvement of

the left main coronary artery. The median BCIS score was 10 (Q1-Q3: 8-12). At a median follow-up of 41 months (Q1-Q3: 28-60 months), there was no significant difference in the primary endpoint between the 2 groups. There was also no significant change in LVEF at 6 and 12 months in either arm. Finally, although KCCQ score and other measures of quality of life improved to a greater degree in the PCI arm, at 6-month follow-up, the between-group differences diminished over time. This may in part have been due to a greater crossover to PCI in the medical therapy-only arm. In the REVIVED-BCIS2 trial it was estimated that the median percentage of completeness of revascularization was 70%. Despite this, the authors found no association between the extent of anatomical complete revascularization or viability-defined complete revascularization and the treatment effect on the primary outcomes or on the likelihood of recovery in LVEF.[71] These findings are similar to previous studies that have failed to show that focal PCI-based revascularization does not prevent future cardiac events in patients with stable CAD. It is possible that the portion of the plaque treated with PCI is not responsible for future plaque destabilization but related to lesions up- or downstream from the original obstruction. Current imaging and computational studies are investigating where the high-risk area is located along the course of a plaque, so revascularization may be more appropriately directed to future culprit sites.[72]

The difference in reported outcomes in the REVIVED-BCIS2 trial and STICHES trial highlight some important considerations. Importantly, there were clear differences in the study design and trial participants that preclude us from directly comparing outcomes (**Table 9**). Patients enrolled in the REVIVED-BCIS2 trial were roughly 10 years older than those in STICH and follow-up was much shorter in the REVIVED-BCIS2 trial. The STICHES trial was conducted >10 years before REVIVED-BCIS2. During that time, the treatment of HF did not include the routine use of angiotensin-neprilysin inhibitors, and few enrolled patients received an implantable defibrillator. Recent pooled analysis of individual patient data from STICHES and REVIVED-BCIS2 have highlighted the impact of changes in medical therapy between these 2 trials. Adjusted event rates were significantly less in the medical therapy arm of REVIVED-BCIS2 when compared with the medical therapy arm in STICHES. Furthermore, adjusted outcomes of patients with CABG in STICHES were significantly worse than patients who received medical therapy alone in REVIVED-BCIS2.[73] Recognizing these differences, one can still conclude that the evidence supports CABG as a revascularization option to manage patients with extensive CAD and a severe ischemic cardiomyopathy to improve survival. Although observational data suggest better outcomes with CABG than PCI for patients with an ischemic cardiomyopathy,[74,75] the potential for selection bias limits our interpretation of these observational studies. Current trials comparing the role of PCI with CABG are ongoing[76] (see the Future Directions section).

The results of these data highlight the complexities in decision making for revascularization in patients with ischemic cardiomyopathy. Although long-term survival is better with CABG compared with medical therapies for patients meeting the inclusion criteria of the STICH trial, given the upfront hazard of CABG in this sick population of patients, one must consider the estimates for long-term survival for each individual case as well as the impact that the newer drugs for HF might have on outcomes. Current data suggest that up to 15% of CABG procedures are performed in patients with significantly impaired LV function and the risk of death or perioperative low cardiac output syndrome/cardiogenic shock are higher in this cohort of patients.[77] With this

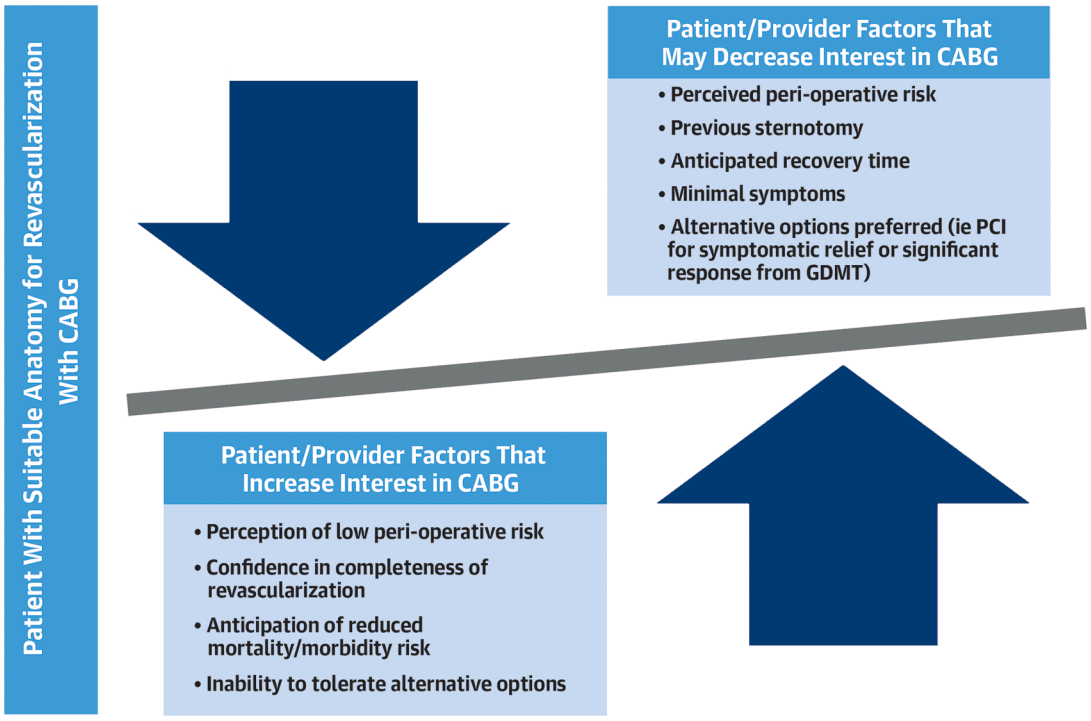
**TABLE 9 Characteristics and Outcomes in the Revascularization Arms of STICH/STICHES and REVIVED-BCIS2 Trials**[48,69,70]

| | STICH/STICHES | REVIVED-BCIS2 |
|---|---|---|
| Baseline characteristics | | |
| Age, y | 60 (54-68) | 70 ± 9 |
| Female | 12 | 13 |
| Diabetes | 39 | 39 |
| Prior MI | 76 | 50 |
| Prior CABG | 4 | 3 |
| LVEF | 27 (22-33) | 27.0 ± 6.6 |
| CCS anginal class 0 | 36 | 66 |
| NYHA functional class III or IV | 37 | 23 |
| TVD | 62 | 38 |
| Significant left main disease | 3 | 14 |
| Proximal left anterior descending artery | 67 | NA |
| Trial characteristics | | |
| Requirements for viability | No | Yes |
| Inclusion post MI | No | No |
| **Primary Endpoint** | **All-Cause Mortality at 5 and 10 Years (n = 610)** | **All-Cause Mortality or Hospitalization for CHF at 2 Years (n = 347)** |
| Time from randomization to treatment, d | 10 (5-16) | 35 (15-57) |
| Years of enrollment | 7/2002-5/2007 | 8/2013-7/2020 |
| Duration of follow-up (months for STICH and REVIVED; years for STICHES) | 56 (48-68)<br>9.8 (9.1-11.0) | 41 (28-60) |

Values are median (Q1-Q3), mean ± SD, or %.

CCS = Canadian Cardiovascular Society; CHF = congestive heart failure; NA = not available; TVD = triple-vessel disease; STICHES = The STICH Extension Study; other abbreviations as in Table 6.

**FIGURE 3** Patient and Provider Factors That Can Influence Decision Making Around Surgical Revascularization in Patients Who Have Suitable Anatomy for CABG


Patient With Suitable Anatomy for Revascularization With CABG
Patient/Provider Factors That May Decrease Interest in CABG
• Perceived peri-operative risk
• Previous sternotomy
• Anticipated recovery time
• Minimal symptoms
• Alternative options preferred (ie PCI for symptomatic relief or significant response from GDMT)
Patient/Provider Factors That Increase Interest in CABG
• Perception of low peri-operative risk
• Confidence in completeness of revascularization
• Anticipation of reduced mortality/morbidity risk
• Inability to tolerate alternative options

CABG = coronary artery bypass grafting; GDMT = guideline-directed medical therapy; PCI = percutaneous coronary intervention.

in mind, when evaluating patients with ischemic cardiomyopathy it is important to determine treatment options based on clinical presentation, anginal symptoms, and coronary anatomy. Additional factors that may influence the decision to proceed with revascularization in high-risk patients with severe HF are the degree of LV dilation, relative thickness of ventricular walls that may represent myocardial scarring, and degree of late gadolinium enhancement on CMR. CABG may be the best choice in patients with triple-vessel disease, or 2-vessel disease involving the left anterior descending artery for patients with a reasonable estimated 10-year survival, but careful selection and management is critical. Even in the presence of suitable anatomy for revascularization by CABG, there are additional patient and provider considerations that can increase or decrease the likelihood of proceeding with CABG (**Figure 3**). Although there is no definite role for PCI as a first-line therapy to improve outcomes or improve EF for patients with an ischemic cardiomyopathy, PCI can be employed to improve quality of life in the short term or improve angina in symptomatic patients with single- or double-vessel disease, not amenable to CABG. The REVIVED-BCIS2 trial reported an improvement in KCCQ scores at 6 months with PCI, with a nominal but persistent difference at 12 months that was not sustained at 24 months.[78] In addition, in the ISCHEMIA trial, patients with HF and LV dysfunction had improved outcomes with an invasive strategy compared with a conservative strategy, as well as improved NYHA functional class, and improvement in the Rose Dyspnea scale.[41] In the REVIVED-BCIS2 trial, few patients had significant angina at baseline, therefore the impact of PCI on angina cannot be ascertained from this trial. However, other trials evaluating the effect of PCI (or an invasive strategy with the intention for revascularization when indicated) have shown improvement in angina scores with an invasive treatment beyond that achieved with medical therapy alone[79,80] among a population of patients with or without LV

**TABLE 10 Considerations in Decision Making Around Revascularization Decisions in HF**

| Domain | Clinical Factors that Suggest High Surgical Risk and/or Low Clinical Benefit | Implications |
|---|---|---|
| LV function | Severely reduced LVEF (<20%) with extensive nonviable myocardium | Minimal likelihood of functional recovery post CABG |
| Coronary anatomy | Diffuse, small vessel disease<br>Poor distal targets<br>Severe calcification of aorta | Incomplete revascularization or technical infeasibility[83] |
| Comorbidities | Advanced CKD (eGFR <30 or dialysis)<br>Severe COPD (FEV1 <50%)<br>Liver cirrhosis<br>Active malignancy<br>Dementia or neurocognitive decline | Elevated perioperative mortality and noncardiac morbidity |
| Frailty | Abnormal frailty assessment<br>NYHA functional class IV<br>Recurrent hospitalizations despite GDMT | Poor rehabilitation potential, low procedural resilience[84] |
| Surgical risk scores[85] | STS score> 10%-15%<br>EuroSCORE II >20% | Indicated high procedural risk, survival benefit uncertain |
| Viability/ischemia testing | No viable myocardium on CMR, PET, or nuclear testing<br>Minimal ischemia on perfusion imaging | CABG may not improve LV function |
| Patient preferences/goals of care | Preference of avoid invasive intervention<br>Focus on quality of life | CABG may not align with patient-centered plans |

CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; FEV1 = forced expiratory volume in 1 second; GDMT = guideline-directed medical therapy; STS = Society of Thoracic Surgeons; other abbreviations as in Tables 1, 2, and 6.

dysfunction (LVEF >35%). Finally, it is important to recognize that both the STICH and REVIVED-BCIS2 trials enrolled stable patients without a recent acute MI. Revascularization with PCI is often the mainstay of therapies for the acute treatment of these patients irrespective of LV dysfunction, and therefore PCI is recommended in patients who have anatomy suitable for PCI to improve outcomes irrespective of the presence or absence of HF.[67]

## CONSIDERATIONS FOR CLINICAL PRACTICE.

- Before advances in medical and device therapy, revascularization with CABG improved outcomes in stable patients with an ischemic cardiomyopathy and severe extensive CAD; however, these studies excluded patients with significant clinical HF.[68,69] All patients with stable CAD and HF should have optimization of medical therapy before surgical revascularization, and it is reasonable to defer revascularization in the absence of angina/high-risk features.
- The most recent 2021 ACC/AHA/SCAI (Society for Cardiovascular Angiography and Interventions) Guidelines for Coronary Artery Revascularization Provide a Class I recommendation for CABG in patients with LVEF <35% and multivessel disease, and a Class IIa recommendation if LVEF is between 35% and 50%.[67]
- Diabetes mellitus is associated with more diffuse and multivessel disease, accelerated atherosclerosis, and increased procedural risk from PCI. Although patients with HF were excluded from the Freedom Trial,[81] a strategy of CABG was superior to PCI in reducing all-cause mortality, MI, and repeat revascularization. Thus, the presence of diabetes represents a key variable in the heart team approach for revascularization, and CABG is recommended over PCI when feasible.[67]
- Clinical data do not support the routine use of PCI to manage patients with an ischemic cardiomyopathy and severe extensive CAD to reduce all-cause mortality and HF hospitalizations.[48]
- PCI as an adjunct to GDMT may improve exercise tolerance and quality of life in the short term, and may reduce symptoms of angina in patients with an ischemic cardiomyopathy based on evidence from unblinded randomized trials.[48,78,79]
- In appropriate patients with an ischemic cardiomyopathy and extensive CAD with anatomy suitable for PCI, physicians may consider PCI when CABG is not an option, although this approach has no supportive trial data to support it.[82] In the absence of angina, routine revascularization by PCI is not recommended. Although the 2021 ACC/AHA/SCAI coronary revascularization guidelines suggest that PCI (in the absence of angina) can be considered when there is evidence of ischemia, high-risk anatomy, or viable myocardium that could benefit from revascularization, the evidence to support this approach remains limited (Table 10).[67]

**TABLE 11 Considerations When Deciding Between Surgical Revascularization and Referral for Cardiac Transplantation in Advanced HF**

| Clinical Considerations That May Favor Surgical Revascularization in Advanced HF | Clinical Considerations That May Favor Cardiac Transplantation in Advanced HF |
|---|---|
| Clear targets for revascularization with LVEF ≥20% | Severely dilated left ventricle with LVEF <20% |
| Young patient with minimal comorbidities and otherwise anticipated good long-term survival | Low probability of significant ventricular recovery following revascularization |
| Ineligible for cardiac transplantation | Pervious sternotomies, and/or older age limiting options for subsequent transplantation in future |
| | Severe right heart failure |

Abbreviations as in Tables 2 and 6.

## THE ROLE ADVANCED THERAPIES IN MANAGING PATIENTS WITH ISCHEMIC CARDIOMYOPATHY

In patients with acute on chronic worsening ischemic heart disease with LVEF <30%, intolerance to targeted GDMTs or dependence on inotropes, work-up for advanced HF therapies, including heart transplantation and durable left ventricular assist device implantation should be undertaken in eligible individuals. In patients being considered for either PCI or CABG with multiple characteristics consistent with advanced HF, the safety and tolerance of the procedure being offered needs consideration when choosing a therapeutic strategy. The adjunctive role of mechanical circulatory support in patients undergoing PCI with low EF is under ongoing exploration across several trials. These results may directly influence the uptake of PCI for high-risk patients with HFrEF and CAD being considered for nonurgent revascularization.[86-88]

The decision to proceed with surgical revascularization over cardiac transplantation is a complex one, and often guided by short-term procedural risks, anticipation of significant ventricular function recovery, expected long-term survival, and patient-provider preferences (Table 11).

Advanced cardiac therapies also can be considered in patients with ischemic cardiomyopathy with intractable angina, even in the absence of clinical HF. The current heart allocation policy in the United States allows a status 4 designation in a 7-status system (1 = highest priority; 7 = inactive on list) to patients with intractable angina due to ischemic heart disease. To meet the requirements to satisfy this designation, candidates must have CAD and CCS IV angina pectoris, which is defined as angina at rest or with any physical activity.[89] Furthermore, it must be deemed that symptoms cannot be adequately treated by a combination of medical therapy and percutaneous or surgical revascularization. In addition, there is a requirement of myocardial ischemia as seen by imaging rather than infarction on perfusion-imaging modalities or extensive scar and fibrosis by CMR.[90] The policy does not require the presence of an end-stage cardiomyopathy or specific LVEF cutoff to meet this designation. Status 4 listings in many regions nationally do not confer high odds of transplantation compared with high-priority statuses, specifically those who are listed status 1 through 3. The policy was created with the assumption that those at highest risk of death or deterioration while on the waitlist, for example, those critically ill on temporary mechanical circulatory support devices or high-dose inotropes, should receive the highest listing priority. Although patients with intractable angina represent a smaller subset of candidates listed for heart transplantation, exception requests for status upgrades are commonly employed strategies to increase the odds of heart transplantation for candidates who otherwise would not confer a high waitlist priority.[91,92] In these patients who have concomitant severe HF, many centers will opt to pursue the status 2 designation to increase odds of transplantation pending meeting the hemodynamic shock criteria requirements and placement of temporary mechanical circulatory support devices. Higher-status patients, compared with status 4 patients who are listed due to refractory angina, have long inpatient lengths of stay and higher costs because of the need for inpatient hospitalization while awaiting heart transplantation.

## GAPS, FUTURE DIRECTIONS

**GAPS.** Despite CAD being a common cause of HF in higher-income countries, there are large knowledge gaps that should be addressed by leveraging advances in trial design including capture of endpoints from routinely collected data, streamlined international trials, big data analysis, and incorporating

**TABLE 12 Ongoing/Planned Trials in CAD and HF**

| Trial | Patient Population | Countries | Randomization | Primary Endpoint |
|---|---|---|---|---|
| STICH 3.0 International Trial (NCT05761067) | Patients with severe CAD, LVEF ≤40% eligible for PCI or CABG | International | PCI vs CABG | All-cause mortality |
| STICH 3C (NCT05427370)[a] | 754 patients with severe CAD and LVEF ≤40% | Led by Canada (multinational) | PCI vs CABG | Time to all-cause mortality, stroke, spontaneous myocardial infarction, urgent repeat revascularization or HF readmission |
| STICH3-BCIS4[a] | 630 patients with severe CAD and LVEF ≤40% | United Kingdom only | PCI vs CABG | Time to all-cause mortality or cardiovascular hospitalization |
| STICH-SWEDEHEART (NCT05329285)[a] | 470 patients with severe CAD and LVEF ≤40% | Led by Sweden (multinational) | PCI vs CABG | Time to death, stroke, nonprocedural MI, or HF hospitalization |
| CABG or PCI in high-risk patients with ischemic heart disease (NCT05534698)[a] | 1,550 patients in "CABG or PCI in high-risk patients with ischemic heart disease" (subgroup with severe CAD and LVEF ≤40%) | Denmark only | PCI vs CABG | Time to all-cause mortality/ stroke/ MI/ hospitalization for HF |
| PROVERB (NCT05532631) | 1,040 patients with severe CAD and LVEF ≤40% | France only | PCI vs CABG | Time to death from any cause, stroke, MI, and unplanned hospitalization for HF or urgent revascularization |
| RESTORE-PCI (NCT05828719) | 900 patients with LVEF <40% and CAD by mandated intracoronary physiology assessment | South Korea only | PCI vs OMT alone | Death, MI, HF hospitalization, LVAD or transplantation |
| BCIS-CHIP-3 (NCT05003817) | 300 patients with severe CAD, LVEF ≤35% undergoing complex PCI | United Kingdom only | Impella vs no Impella | Hierarchical outcome of death, stroke, spontaneous MI, cardiovascular hospitalization or periprocedural MI |
| PROTECT-IV (NCT04763200) | 1,252 patients with non-STEMI and EF ≤40% or STEMI with LVEF ≤30% | International | Impella vs no Impella | Death, stroke, MI, or hospitalization for cardiovascular causes |
| PROFID-EHRA (NCT05665608) | 3,595 patients with HF, previous MI, and LVEF ≤35% | Europe | ICD vs no ICD | All-cause mortality |
| CROSS-HF (ISRCTN12403403) | 3,000 patients with new onset of HF in past 12 mo | United Kingdom only | CTCA vs stress CMR vs invasive coronary angiogram | Time to all-cause death, MI, HF hospitalization |
| ISCHEMIA-LVD (NCT06566183) | 1,200 patients with LVEF ≤40% and multivessel CAD | International | 1:2:2 GDMT: GDMT and CABG: GDMT and PCI | Composite cognitive score<br>HF-related health status<br>Composite of death, MI, stroke, and hospitalization for HF |
| IMPROVE-ICMP (NCT06930092) | 158 patients with LVEF <40% and multivessel CAD | South Korea only | Physiology-and imaging-guided PCI vs OMT alone | LVEF by CMR at 6 mo |
| MASS-VI (HF)[93] | 600 patients with LVEF <35% and multivessel CAD | Brazil | CABG vs OMT | Death, nonfatal MI, stroke, and unstable angina |

[a]Trials that are part of the international STICH 3.0 International Trial.

BCIS-CHIP3 = Controlled trial of High-risk coronary Intervention with Percutaneous left ventricular unloading; CROSS-HF = CROSS sectional versus invasive imaging in patients with heart failure; ICD = implantable cardioverter-defibrillator; IMPROVE-ICMP = RestoratIon of Myocardial Function by PeRcutaneous cOronary interVEntion in Patients With Ischemic CardioMyoPathy; ISCHEMIA LVD = International Study of Comparative Health Effectiveness With Medical and Invasive Approaches-Left Ventricular Dysfunction Trial; LVAD = left ventricular assist device; MASS-VI (HF) = Evaluation of a randomized comparison between patients with coronary artery disease associated with ischemic cardiomyopathy submitted to medical or surgical treatment; OMT = optimal medical therapy; PROFID EHRA = Prevention Of Sudden Cardiac Death After Myocardial Infarction by Defibrillator Implantation; PROTECT IV = Impella-Supported PCI in High-Risk Patients With Complex Coronary Artery Disease and Reduced Left Ventricular Function; PROVERB = Percutaneous Coronary RevascularizatiOn VERsus Coronary-Artery Bypass Grafting for Multivessel Disease in Patients With Left Ventricular Dysfunction; RESTORE-PCI = Revascularization Versus Medical Treatment in Patients With Ischemic Left Ventricular Dysfunction; STEMI = ST-segment elevation myocardial infarction; STICH 3.0 = The CABG or PCI in Patients With Ischemic Cardiomyopathy [STICH] 3.0 International Trial Consortium; STICH3-BCIS4 = Surgical Treatment for Ischemic Heart Failure-British Cardiovascular Intervention Society; STICH3C = The Canadian CABG or PCI in Patients With Ischemic Cardiomyopathy Trial; STICH-SWEDEHEART = CABG or PCI in Patients With Ischemic Cardiomyopathy; other abbreviations as in **Tables 1, 2, and 6**.

outcomes of greatest interest to patients. Imaging and biomarker characterization have yet to be proven to identify patients who will benefit from revascularization in the modern era. Development of personalized management strategies requires robust data derived from deeply phenotyped, heterogeneous patients. Treatments demonstrated to be effective in randomized trials, including optimized timing of implementation, should be communicated to patients with validated shared-decision tools. Patients typically rank longevity the highest priority, but functional status, including freedom from strokes and cognitive dysfunction, are important, especially in an aging population.

**TABLE 13 Selected Gaps and Considerations for Future Clinical Research**

| | |
|---|---|
| Gaps: selected clinical questions unanswered by clinical trials | Revascularization in HFpEF: no trials of PCI vs CABG vs medical therapy for revascularization of epicardial disease in HFpEF |
| | Microvascular disease: no trials of treatment of microvascular disease in HFpEF or HFrEF |
| | Lipid lowering in HFpEF: no trials of lipid lowering in HFpEF |
| | Revascularization in hospitalized HF (not STEMI-related cardiogenic shock); absence of RCTs in hospitalized HF |
| | Screening HFrEF for CAD/ischemia followed by initial medical therapy alone vs revascularization with PCI vs CABG |
| Future directions: selected considerations of future trials | Sham-controlled trials (especially in assessment of treatment effects on health status/quality of life) |
| | AI using big data to deeply phenotype patients beyond "HFrEF" and "HFpEF" to determine subpopulations that may benefit from specific interventions |
| | Restudy of "viable myocardium" and "ischemia" in HF to determine parameters that indicate response to revascularization |
| | Trials to investigate underserved populations (including women, low socioeconomic class) |

AI = artificial intelligence; RCT = randomized controlled trial; other abbreviations as in Tables 1, 2, 6, and 11.

Ongoing and planned trials (Table 12) will provide data on several key areas discussed in this report, including the following:

- The role of revascularization and comparison of PCI and CABG for HFrEF. The STICH 3.0 (The CABG or PCI in Patients With Ischemic Cardiomyopathy [STICH] 3.0 International Trial Consortium) international suite of pragmatic, streamlined trials comparing PCI with CABG in HF will build on data from REVIVED (PCI vs medical therapy) and STICH (CABG vs medical therapy). The STICH 3.0 trials include chronic ambulatory HF with LVEF ≤40% as well as patients with non-ST-segment elevation myocardial infarction (STEMI) with LVEF ≤40%.
- Physiology-guided PCI vs medical therapy in LVEF <40%.
- CABG plus optimal medical therapy (OMT) vs OMT alone.
- Mechanical circulatory support for high-risk PCI.
- ICD for ischemic HFrEF.
- The choice of imaging modality to determine diagnosis and inform CAD management decisions.

**FUTURE DIRECTIONS. Role of broader screening and use of revascularization in HFrEF.** Patients with HF seldom undergo testing for CAD and even less often undergo revascularization.[28] It is unknown whether broad testing for ischemia or CAD followed by routine revascularization, with or without viability testing, will improve survival and/or patient-centered outcomes in the era of modern GDMT.

Revascularization trials in hospitalized patients have focused on STEMI-related cardiogenic shock and not on the large number of patients hospitalized with decompensated HF. Randomized controlled trials investigating revascularization strategies in this high-risk group have yet to be conducted.

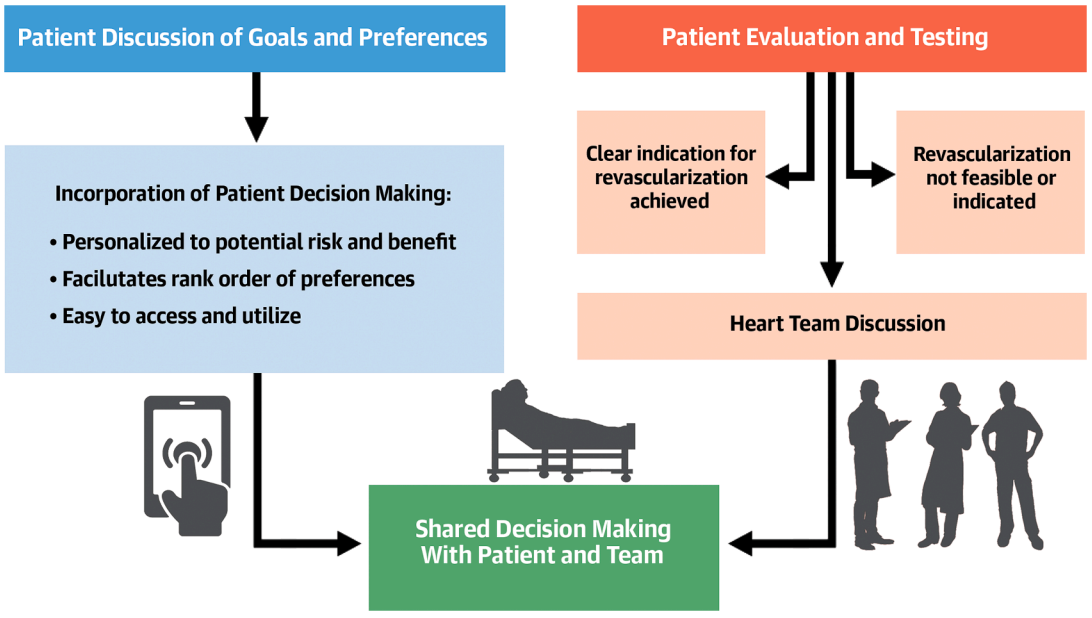
**Management of CAD in HFpEF.** Despite observational studies reporting that many patients with HFpEF have obstructive epicardial CAD, there is an absence of randomized trials investigating improvement in HFpEF symptoms or clinical outcomes with revascularization.[94] There is a need for trials to determine the effect of various modalities to treat CAD in HF (ie, PCI, CABG, or medical therapy alone).

**Microvascular disease.** In HFpEF a potential central pathological process is microvascular CAD. Microvascular disease is also common in HFrEF. Therapies are needed for microvascular dysfunction and should be tested in HF.

**Medical management of CAD in HF.** Although statins play an important role in the management of documented atherosclerosis, prior MI, elevated low-density lipoprotein, and diabetes or chronic kidney disease, there is no evidence of benefit in HF-specific outcomes, and contemporary trials are lacking in HF. PCSK9 inhibitors did not prevent HF hospitalizations in a meta-analysis of 23 trials.[62] No trial has been conducted to investigate statins in established HFpEF. Large CV outcome trials such as LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results), SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes), and REWIND (Dulaglutide and cardiovascular outcomes in type 2 diabetes: a double-blind, randomized placebo-controlled trial)[95-97] have shown that glucagon-like peptide 1 receptor agonists can reduce major CV events in patients with diabetes and established CAD or other high-risk features, and have demonstrated benefit in patients with obesity and HFpEF; however, there are limited data to guide their use in patients with HFrEF.[98,99]

Clinical trials of aspirin vs placebo in HFrEF are limited and inconclusive and absent for HFpEF. There has been much debate about the value of aspirin in HF with some proposing detrimental effects.[57,58]

**FIGURE 4** Incorporating Patient Preferences and the Use of Patient Decision-Making Aids into Shared Decision Making for Revascularization in HF


Patient Discussion of Goals and Preferences
Patient Evaluation and Testing
Clear indication for revascularization achieved
Revascularization not feasible or indicated
Incorporation of Patient Decision Making:
• Personalized to potential risk and benefit
• Facilutates rank order of preferences
• Easy to access and utilize
Heart Team Discussion
Shared Decision Making With Patient and Team

Abbreviation as in Figure 1.

**Placebo-controlled trials.** Recent CV trials have demonstrated a substantial placebo effect and also that placebo-controlled trials are feasible and often appropriate, especially when assessing endpoints such as health status, quality of life, angina, or HF hospitalization. Interventional placebo-controls will become increasingly used in trials in CAD and HF.

**Big data/artificial intelligence.** The terms "HFrEF" and "HFpEF" are broad categories including many patients with hearts that vary in terms of extent of epicardial disease, microvascular disease, myocardial scar, and viability. These hearts also vary in terms of right ventricular function and valvular disease as well as many extra-cardiac factors. Future artificial intelligence to deeply phenotype patients beyond "HFrEF" and "HFpEF" using clinical, biomarker, and imaging data to determine subpopulations may benefit from specific interventions. Detailed multimodality imaging of coronary arteries, the left and right ventricular myocardium, and valves are likely to identify subpopulations appropriate for targeted therapies.

Previous studies deriving and validating imaging parameters such as viability in HF have been conducted in small populations. Imaging studies in HF are likely to become larger to carefully establish parameters that can guide therapy.

**Evaluation of patient-centric decision tools.** Shared decision making and a deeper understanding of the goals and preferences of our patients are important elements to consider when making decisions around revascularization in high-risk patients.[100] Such an approach can help streamline the identification of patient values. This has been done in the context of previous clinical trials, such as the ISCHEMIA trial, whereby a patient decision aid was developed to provide patient-specific estimates of outcomes for invasive vs conservative management of chronic coronary disease.[101] Thus, aid was suggested to be most impactful when used collaboratively with clinical teams. Given the complexity and uncertainties around decision making, it is important that patient preferences are incorporated into decision making for revascularization in HF (Table 13, Figure 4).

## CONCLUSIONS

In 2025 too little is known about the optimal use of imaging to guide treatment of patients with CAD and HF. Advances in imaging may establish subpopulations with CAD and HF who have more or less to gain from different therapeutic strategies. There are also limited data to define the role, timing, and type of revascularization in HFrEF and an absence of data in HFpEF. Many knowledge gaps could be filled with large, randomized trials that use streamlined, pragmatic designs and possible big data, platform trials, and Bayesian interim monitoring and analytic plans.[102]

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